

*Sub 32*  
nitrogen attached to the 6' carbon; R<sub>11</sub>, R<sub>12</sub>, R<sub>13</sub>, and R<sub>14</sub> are each hydrogen or halogen, where R<sub>a</sub> is an alkyl, carboxyalkyl, aminoalkyl, cycloalkyl, aryl, or arylalkyl having from 1 to 10 carbon atoms, and Z [includes] represents a linker plus the conjugated substance.

*A3* 12. (Amended) The conjugate as in claim 10 wherein the linkage between the fluorophore and conjugated substance [includes] has a phosphate ester.

### REMARKS

Claims 1-20 were at issue. Claims 1-20 were rejected. Claims 1, 10 and 12 have been amended. The Examiner made the following rejections:

- (1) Claims 1-20 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicant regards as the invention.
- (2) Claims 1-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. patent 4,647,675 to Mayer *et al.*, in view of U.S. patent 4,900,686 to Arnost *et al.* and U.S. patent 5,846,737 to Kang.

Applicants believe that the present amendments and the following remarks traverse the Examiner's rejection of the claims. These remarks are presented in the same order as they appear above.

#### 1. The Claims Are Definite

The Examiner is reminded that "[c]laims of a patent application *are to be construed in the light of the specification* and the understanding thereof by those skilled in that art to whom they are addressed'." *Application of Salem*, 553 F.2d 676, 683, 193 USPQ 513 (CCPA 1977) (quoting *In re Myers*, 410 F.2d 420, 425 (CCPA 1969) with emphasis added in *Salem*). Furthermore, "[t]he patent law 'allows the inventor to be his own lexicographer,' " *Loctite Corp. v. Ultraseal Ltd.*, 781 F.2d 861, 867, 228 USPQ 90, 93 (Fed. Cir. 1985) (quoting *Autogiro Co. of America v. United States*, 384 F.2d 391, 397, 155 USPQ 697, 702 (Ct. Cl.

1976)). The Applicant, therefore, is free to introduce any descriptive term or phase, "functional" or otherwise, into the claims so long as these descriptors are adequately defined in the Specification. Moreover, the Examiner is reminded that, "the breadth of a claim is not to be equated with indefiniteness." MPEP § 2173.04 [citing to: *In re Miller*, 411 F.2d 689, 169 USPQ 597 (CCPA 1971)]

**A. The Specification Provides Explicit Definitions**

The Examiner maintains that,

"[c]laims 1-2 are written in functional language and therefore, broader than the enabling disclosure. For example claim 1 recites, 'conjugating the fluorephore with an organic compound', and claim 2 recites, 'reacting the organic compound and the fluorophore under covalent bond forming conditions'. Therefore, claims 1-9, are indefinite."<sup>1</sup>

The Applicant respectfully submits the Examiner need look no further than the Specification of the Application as filed to find explicit definition for theses allegedly "indefinite" terms. For example,

"The conjugation is preferably via a phosphoramidite linkage when synthesizing labeled oligonucleotides, and may be by a variety of the known protein conjugation chemistries when synthesizing labeled peptides or labeling"<sup>2</sup>

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"By using protein conjugation reagents known to those skilled in the art, amino acid and peptide conjugates of the invention can be made."<sup>3</sup>

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"As will be readily understood by persons skilled in the art of protein conjugation, a variety of protein conjugation derivatives may be used to target amino acid reactions. A number of protein conjugation reagents and techniques are, for example, described by Hermanson in *Bioconjugate Techniques*, Academic Press, San Diego, California 1996. Further, since cells and viruses contain proteins on their surface membranes or viral coats, cells or viral particles can be labeled by practicing this invention. An example of a well-known protein conjugation reagent, one suitable functional group for inclusion

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<sup>1</sup> Office Action mailed August 24, 2000, page 2.

<sup>2</sup> Application as filed, page 3, ll, 25-28.

<sup>3</sup> Application as filed, page 8, ll, 12-13.

in the Ra' substituent is succinimidyl ester, which readily reacts with primary amines."<sup>4</sup>

In view of these explicit teachings cited in the Specification, the Applicants submit that the use of "conjugating the flurophore with an organic compound" and "reacting the organic compound and the fluorophore under covalent bond forming conditions" is definite and, therefore, entirely appropriate in the claims. Moreover, the Applicants take exception to the Examiner's suggestion that the, "claims must recite the reagents, the reaction times and conditions involved in the process."<sup>5</sup> 35 U.S.C. § 112 ¶ 2 requires that the claims "particularly [point] out and distinctly [claim] the subject matter which the applicant regards as his invention." However, it is well settled law that "a claim need not 'describe' the invention, such description being provided by the specification's disclosure section." *Orthokinetics Inc. v. Safety Travel Chairs Inc.*, 806 F.2d 1565, 1576, 1 USPQ 2d 1081, 1088 (Fed. Cir. 1986). In this respect, the Applicants respectfully suggest that the Examiner need look only to the numerous "Examples" (in the application as filed) for reaction "specifics" (e.g. reagent molarity and reaction conditions).

#### **B. The Claims Do Not Recite Indefinite Limitations**

The Examiner also rejects claims 1-9 as indefinite for, "having a broad range or limitation together with a narrow range of limitation that falls within the broad range or limitation (in the same claim)."<sup>6</sup> Applicants disagree. Specifically, "[a] group reactive to derivatization" is not a narrow range of limitation that falls within the broader range of "non-hydrogen substituents". That is to say, "[a] group reactive to derivatization" is an additional limitation that further qualifies the claim element Ra' and is distinct from the limitation "non-hydrogen substituents" which qualifies both claim elements R<sub>a</sub> and R<sub>a</sub>'. In support of this interpretation of the claims, Applicants note that the limitations in questions **are not** linked by the phrase "such as". That is to say, "[a] group reactive to derivatization" is not offered as an exemplar / further limitation of "non-hydrogen substituents". The

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<sup>4</sup> Application as filed, page 13, ll, 15-23.

<sup>5</sup> Office Action mailed August 24, 2000, page 2.

<sup>6</sup> *Id.*

limitations in question are distinct and, therefore, the claims are compliant with the directives set out in MPEP 706.03(d).

**C. The Applicants Have Amended Claims To Advance Business Interests**

Without acquiescing to the Examiner's argument, and in order to advance their business interests, the Applicants have amended the claims while expressly reserving the right to prosecute the claims as originally filed (or claims similar thereto) in a subsequent continuation application.

**2. The Claims Are Not Obvious Under 35 U.S.C. § 103(a)**

**A. The Examiner Fails to Make A *Prima Facie* Case of Obviousness**

Claims 1-20 stand rejected as allegedly unpatentable over U.S. patent 4,647,675 to Mayer *et al.*, in view of U.S. patent 4,900,686 to Arnost *et al.* and U.S. patent 5,846,737 to Kang. The Examiner is reminded that a *prima facie* case of obviousness requires citation to a combination of references which (a) disclose the elements of the claimed invention, (b) suggests or motivates one of skill in the art to combine those elements to yield the claimed combination, and (c) provides a reasonable expectation of success should the claimed combination be carried out. Failure to establish any one of the these three requirements precludes a finding of a *prima facie* case of obviousness, and, without more, entitles Applicant to allowance of the claims in issue. *See, e.g., Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990).

The Applicant respectfully submits the Examiner has failed to establish each of the three elements of a *prima facie* case of obviousness. In addressing this rejection, Applicants focus on independent Claims 1 and 10 since non-obviousness of an independent claim necessarily leads to non-obviousness of claims dependent therefrom. §MPEP 2143.03.

**i. No Motivation to Combine the References**

A proper analysis, in view of 35 U.S.C. §103(a), demands the references cited by the Examiner be considered as whole and must suggest the desirability and, thereby, the obviousness of making the combination. *Hodash v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143, n. 5, 229 USPQ 182, 187, n.5 (Fed. Cir. 1986). Applicants submit that references

cannot be considered collectively until the Examiner points to some motivation to combine said references. This analysis prevents the Examiner from using the instant Specification to reconstruct, in hindsight, the invention as claimed. The Federal Circuit, in a recent decision, articulated the policy behind this analysis:

To prevent the use of hindsight based on the invention to defeat patentability of the invention, this court requires the examiner to show a motivation to combine the references that create the case of obviousness. In other words, the examiner must show reasons that the skilled artisan, confronted with the same problems as the inventor and with no knowledge of the claimed invention, would select the elements from the cited prior art references for combination in the manner claimed.

*See In re Rouffet et al.*, 149 F.3d 1350, 47 USPQ2d 1453 (Fed. Cir. 1998).

The above referenced prior art does not suggest the desirability of making the combination of elements which recapitulates the invention as claimed. In the Office Action mailed on June 6, 1999, the Examiner stated,

"[o]ne of ordinary skill in the art would have known to conjugate the rhodamine dyes of Mayer *et al.*, at the time the instant invention was made. . . [t]he motivation is to make additional florescent conjugates."<sup>7</sup>

The Applicant respectfully submits the Examiner presents bald conclusions in place of reasoned motivation, as articulated by the Federal circuit, to combine the cited art.

As a threshold observation, the Applicant's note *the Examiner admits* that, "Mayer *et al.* do not teach the process of making the [Applicants'] conjugates".<sup>8</sup> That is to say, Mayer *et al.* **are completely silent** on the methods as claimed in the instant application.

In fact, the only "use" for the compound disclosed by Mayer *et al.* is directed to the dying of fibers and the preparation of printing inks. Specifically, Mayer *et al.* teach,

"[t]he compounds of the formula I are useful for dyeing anionically modified fibers, for the preparation of printing pastes and printing inks, and for dyeing leather and plastics and in particular paper stocks. Surprisingly, these compounds can also be used for dyeing bleached (wood-free or low-wood) pulps in brilliant red hues."<sup>9</sup>

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<sup>7</sup> Office Action Mailed August 24, 2000, page 6.

<sup>8</sup> Office Action Mailed August 24, 2000, page 4.

<sup>9</sup> U.S. Patent 4,647,657 to Mayer *et al.*, Col. 3, ll 20-25.

In this respect, U.S. patent 4,647,675 to Mayer *et al.* must be regarded as non-analogous art *vis-a-vis* the present invention. That is to say, the law requires that the art cited by the Examiner be directed to the essentially the same function and purpose as the claimed invention. See *In re Deminski* 796 F.2d 436 (Fed. Cir. 1986). If the cited art does not have the same purpose, an inventor would be less motivated to consider it. *In re Clay*, 966 F.2d 656 (Fed. Cir. 1992). Applying these legal standards, it is clear that compositions "useful for dyeing paper stocks",<sup>10</sup> as described by Mayer *et al.*, are not relevant or dispositive to the present **methods** for conjugations as claimed in the present invention.

The Examiner states that U.S. patent 4,900,686 to Arnost *et al.* "teach several linking groups such as esters, aldehydes, cyanates, sulfide, etc." The Examiner is reminded, however, that the Applicants are not claiming, in the present application, linking groups as a composition of matter. That is to say, Arnst *et al.*, are silent on the specific *methods* of conjugation claimed in the present invention such that an organic compound **is not conjugated** through the Ra' substituent set out in the invention as claimed.

U.S. patent 5,846,737 to Kang *teaches away* from the present invention. That is to say, Kang is directed exclusively to conjugates of *sulforhodamine*. In view of the present invention, the sulphate group on a sulforhodamine causes an unfavorable stearic interaction which substantially prevents the conjugation of an organic compound with a fluorphore as claimed. The Examiner is reminded that a reference which teaches away from the invention as claimed is evidence the *non-obviousness* of the present invention. That is to say, the Federal Circuit has said that discovering a method in the face of prior art which suggests that such a method would produce unacceptable results is the antithesis of obviousness. See, *In re Hedges*, 228 USPQ 685, 687 (Fed. Cir. 1986).

Despite these shortcomings, the Examiner attempts to fill the void left by the non-relevant teachings of Mayer *et al.* with a conclusory argument to suggest the combination of the cited prior art. Specifically, the Examiner sets out the proposition that, "the use of analogous reactants in a well known process is *prima facie* obvious. . .[t]he motivation is to make additional fluorescent conjugates." The *Rouffet* court, however, admonishes against such an unsupported statement. Indeed, the Federal Circuit stated:

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<sup>10</sup> See, Abstract of U.S. Patent 4,647,657 to Mayer *et al.*

The Board did not . . . explain what specific understanding or technological principal within the knowledge of one of ordinary skill in the art would have suggested the combination. Instead, the Board merely invoked the high level of skill in the art. If such a rote invocation could suffice to supply a motivation to combine, the more sophisticated scientific fields would rarely, if ever, experience a patentable technological advance. Instead, in complex scientific fields, the Board could routinely identify the prior art elements in an application, invoke the lofty level of skill, and rest its case for rejection. To counter this potential weakness in the obviousness construct, the suggestion to combine requirement stands as a critical safeguard against hindsight analysis and rote application of the legal test for obviousness. *Rouffet*, 47 USPQ2d at 1458.

Contrary to the Examiner's opinion, the prior art provides no motivation to combine the references to teach the claimed invention the claimed method of conjugating a fluorophore with an organic compound. That is to say, obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. MPEP 2143.01 at 2100-98, citing *In re Fine*, 837 F.2d 1071, 11 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). Unsupported speculation that a given references might be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. MPEP 2143.01 at 2100-98, citing *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990).

The Examiner suggests there is a motivation to make "additional fluorescent conjugates", but has failed to provide any document any source for this motivation to induce one skilled in the art to prepare these speculative conjugates. Once again, the Examiner is reminded that "[t]he teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure." MPEP 2142 / 2143, citing *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). Accordingly, Claims 1-20 should be passed to allowance.

**ii. The Combined References Do Not Teach Each Element of the Claims**

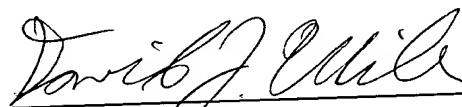
Even if the references are improperly combined, the references do not teach each and every element of the invention as claimed. The references cited by the Examiner do not teach conjugating a fluorophore (with the structural limitation set out in claims 1 and 10) with an organic compound to be labeled such that the same organic compound is conjugated through the  $R_a$  group of the fluorophore, the resultant conjugate being fluorescent upon excitation with light of a determinable wavelength.

Because the cited references fail to disclose all the limitations of Independent Claims 1 and 10, a *prima facie* case of obviousness is not established as to said Independent Claims and any Claims dependent therefrom.

**CONCLUSION**

Applicant believes that the arguments set forth above traverse the Examiner's rejections and therefore request that these grounds for rejection be withdrawn for the reasons set forth above. Should the Examiner believe that a telephone interview would aid in the prosecution of this application, Applicant encourages the Examiner to call the undersigned collect at 617.252.3353.

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